UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,500	04/11/2001	Glenn Richard Carlson	98-039B	2455

7590 09/09/2004

ReoGene Holdings,Inc
ReoGene Holdings,Inc
2650 Eisenhower Avenue
Norristown, PA 19403

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/832,500	CARLSON ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/12/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 11 April 2001 as a divisional of 09/315,451 filed 20 May 1999, which is a continuation-in-part of 09/210,010 filed 11 December 1998, which claims benefit of provisional application 60/089,546 filed 17 June 1998. The preliminary amendment filed concurrently with the application has been entered. Claims 1-17, 19 and 20 are presently pending.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 18 June 2004 is acknowledged. However, upon further consideration of the claims issued in the parent application, it is apparent that claims 1 and 2 therein fully encompass the subject matter of each of Groups I-III. As the subject matter of all three Groups has already been examined, the groups will be rejoined and examined together herein. The restriction requirement set forth in the 18 May 2004 Office Action is hereby withdrawn. Claims 1-17, 19 and 20 are presently under consideration.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant application, the ligand molecule of the claims is subject to several limitations and provisos not contemplated in either the 09/210,010 application or the 60/089,546 (for example, compare claim 1 of the instant application to claim 1 of the '010 and '546 applications). As the claims of the instant application are directed to methods of using genus of ligands having limitations not explicitly or implicitly contemplated in the parent applications, the claims do not enjoy support of the '010 and '546 applications. Therefore, the effective filing date of the instant claims is 20 May 1999, *i.e.*, the date of filing of the 09/315,451 application.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 2, 6, 10 and 14 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5, respectively, of prior U.S. Patent No. 6,258,603. This is a double patenting rejection.

The claims of the instant application are identical to the claims of the '603 application (*i.e.*, recite the same limitations) and therefore are of identical scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to modulate gene expression *in vitro* or in a plant, does not reasonably provide enablement for the method practiced in animals *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims are directed to a method to modulate exogenous gene expression comprising contacting an ecdysone receptor complex comprising a ligand with a DNA construct comprising an exogenous gene under the control of a response element. In some claims, the subject of the claims is limited to being other than a plant, or to being a mammal. With regard to using the claimed invention in a multicellular

organism other than a plant *in vivo*, the specification contemplates only gene therapy (beginning in the first full paragraph on page 13 and continued through the first paragraph on page 15). As the specification must teach the skilled artisan how to make and use the claimed invention and the only use contemplated for the claimed method in intact animals is gene therapy, it is incumbent upon the disclosure of the application to teach the skilled artisan how to practice the claimed invention in animals such that it can be used for gene therapy.

State of the prior art and level of predictability in the art: At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (*e.g.*, adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, "... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene

therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error

for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross *et al.* Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future"**, beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis

for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly,

mechanisms of collateral growth by exogenous growth factors are still unclear…[a]dditional factors…may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency…" (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers…in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues…resembling the characteristics of leaky haemangiomas…" (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

With particular regard to the ecdysone promoter systems used in the instant invention, the art teaches that, at the time of filing, therapeutic use of the promoters remained under investigation and was not considered enabled. For example, Graham (2002) *Expert Opin. Biol. Ther.* 2:525-535 teaches, "[w]hile the initial indications are promising, the toxic, carcinogenic and teratogenic potential of ecdysteroids and other EcR agonists intended for clinical use as transgene inducers obviously require more thorough investigation, and this becomes especially necessary if prolonged exposure is envisaged" (first full paragraph on 532) and "[t]he recombinant expression of EcR in mammalian cells, often in conjunction with rRXR

overexpression, may have unintended-and as yet undiscovered-effects on host cell physiology" (paragraph bridging the left and right columns on page 532).

Thus, the relevant art teaches that at the time of filing achieving sustained gene expression *in vivo* was generally problematic, and therapeutic application of inducible promoters was not routine in the art.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure fails to provide a single working example of the claimed method practiced in an animal *in vivo*. Although, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. As the teachings cited above clearly establish the gene therapy art as unpredictable, the specification must disclose the claimed method in such a manner that one skilled in the art would be able to practice the method for its intended purpose (*i.e.*, gene therapy) without having to engage in undue experimentation. However, the guidance in the specification with regard to practicing the method in an animal *in vivo* is limited to lists of potentially therapeutic nucleic acid constructs (*e.g.*, page 13) and generic statements such as, "[s]uitable routes of administering the pharmaceutical preparations include oral, rectal, topical…[etc.]. The specification provides no specific guidance to address the myriad of problems encountered in developing therapeutically viable methods involving exogenous gene expression.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods *in vivo* for the purpose contemplated in the specification without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to make and use the invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

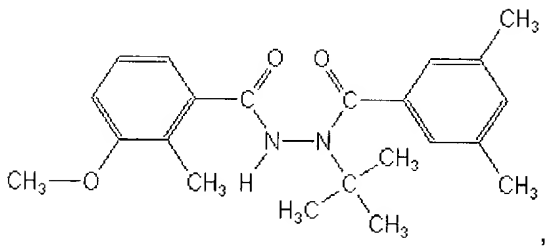
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-17 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Albertsen *et al.* US Patent No. 6,504,082 (effective filing date 10 September 1998).

Albertsen *et al.* teaches a method to modulate exogenous gene expression (see especially the third and fourth paragraphs in column 14) comprising contacting a complex comprising a

DNA binding domain, a ligand binding domain, a transactivation domain and a ligand (see especially the first full paragraph in column 13) with a DNA construct comprising the exogenous gene under the control of a response element (see especially the second paragraph in column 14). Thus, the method of Albertsen *et al.* comprises each of the method steps of independent claims 1-3 and 5. In example 2, Albertsen *et al.* teaches the method for producing a polypeptide which comprises selecting a cell that is substantially insensitive to exposure to the ligand (see especially the NosCLO only and Reporter only controls in Table 1), introducing a DNA construct comprising an exogenous DNA encoding a polypeptide and a response element and an ecdysone receptor complex and exposing the cell to the ligand, which method comprises all of the steps of the method according to independent claim 4.

Further, Albertsen *et al.* teaches that the methods disclosed therein can be practiced in a variety of hosts including microorganisms (*i.e.,* other than a plant) according to claims 3 and 5, and fungi according to dependent claim 20. Albertsen *et al.* also teaches a chimeric ecdysone receptor complex (see especially the first full paragraph in column 13) and a DNA construct comprising a promoter (see especially the third paragraph in column 14) according to dependent claims 14-17. Finally, Albertsen *et al.* teaches that a preferred embodiment of the ligand is methoxyfenozide (IUPAC: *N*-*tert*-butyl-*N*′-(3-methoxy-*o*-toluoyl)-3,5-xylohydrazide) having the structure:



which meets the structural limitations of the ligand of the instant claims (see especially column 18, line 15-16) including dependent claims 6-13.

Thus, Albertsen *et al.* teaches a method comprising all of the elements of the instant claims 1-17 and 20. Therefore, the claims are anticipated by Albertsen *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

Jasemine C. Chambers

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600